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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 :		(11) International Publication Number: WO 93/00383
C08G 65/34, A61K 9/06, 9/107	A1	(43) International Publication Date: 7 January 1993 (07.01.93)

(21) International Application Number: PCT/US92/05195

(22) International Filing Date: 18 June 1992 (18.06.92)

(30) Priority data:
718,187 20 June 1991 (20.06.91) US

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(81) Designated States: AT, AU, BB, BG, BR, CA, CH, CS, DE, DK, ES, FI, GB, HU, JP, KP, KR, LK, LU, MG, MN, MW, NL, NO, PL, RO, RU, SD, SE, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, MC, NL, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: PULSED RELEASE OF HIGH MOLECULAR WEIGHT THERAPEUTIC AGENTS FROM BIOERODIBLE POLYMER COMPOSITIONS

(57) Abstract

Pharmaceutical compositions for the delivery of high molecular weight therapeutic agents such as peptide drugs are provided. Drug delivery from these compositions is pulsed release in nature; the compositions contain at least one hydrophobic, bioerodible polymer that undergoes bulk hydrolytic degradation and restricts diffusion of the therapeutic agent prior to polymer degradation. In a preferred embodiment, the compositions contain a plurality of such polymers, each of which undergoes hydrolysis at a different rate.

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PULSED RELEASE OF HIGH MOLECULAR WEIGHT THERAPEUTIC AGENTS FROM BIOERODIBLE POLYMER COMPOSITIONS

Technical Field

The present invention is in the field of polymer chemistry and drug delivery, and concerns the use of certain bioerodible polymers in pharmaceutical compositions for the delivery of high molecular weight therapeutic agents. The invention is primarily directed to soft dosage forms such as bioerodible ointments, gels, creams and the like, which enable pulsatile delivery of the drug contained therein.

Background of the Invention

The continuing advances in genetic engineering are making available an ever-increasing number of peptide drugs. The vast majority, however, are not orally active, and must be administered in other ways. A number of alternative modes of administration, e.g., nasal, rectal and transdermal, are under active development. However, the bioavailability by these routes is usually low and reproducibility poor. Further, these approaches are limited to small peptides, usually containing less than twenty amino acid residues.

Additionally, there is growing evidence that continuous delivery may not be the optimal delivery regime for all peptides but that pulsatile delivery may in many cases be preferred. Thus, a therapeutic dosage form that can be easily implanted subcutaneously, intramuscularly or intraperitoneally and which is capable

of releasing the peptide in a controlled, pulsatile manner is desirable.

Development of drug delivery systems for high molecular weight drugs such as peptides has been plagued by a plethora of problems. Among these are the high molecular weight of peptides which makes release by Fickian diffusion impractical, the instability of peptides in concentrated aqueous solutions and in certain hydrophobic environments, and the sensitivity of these molecules which can make fabrication of the device without disturbing tertiary structures very difficult.

For this reason, the development of hydrophobic materials that have a paste-like consistency at room temperature or that have softening temperatures below about 50°C is of great interest because high molecular weight therapeutic agents can be mixed into such materials at room temperature or at temperatures that are low enough so that the mixing procedure does not adversely affect the biological activity of the therapeutic agent.

When a high molecular weight therapeutic agent is mixed into such polymers, it is unable to diffuse from the polymer by simple Fickian diffusion because diffusion rate is a function of the molecular weight of the therapeutic agent (and at molecular weights above approximately 1,000 Daltons, the rate of Fickian diffusion becomes vanishingly small). Thus, the therapeutic agent is essentially immobilized in the polymer matrix.

However, polymers that contain hydrolytically labile linkages result in a gradual bulk hydrolysis when exposed to the moist environment encountered within the mammalian tissue. This slow bulk hydrolysis results in a gradual reduction of the molecular weight within the mass of the polymers and, as a consequence of this lowering of

molecular weight, the rate of Fickian diffusion of the high molecular weight therapeutic agent begins to increase until a critical molecular weight is reached where substantial release by Fickian diffusion takes place. At that point, the high molecular weight therapeutic agent is no longer immobilized in the polymer matrix but is released at a relatively rapid rate.

The present invention involves the use of at least one, preferably a combination of such bioerodible polymers--each of which undergoes bulk hydrolysis--to give a composition that has an ointment-like consistency at room temperature or that has a softening point below about 50°C, as described above. Preferably, the individual bioerodible polymers of the composition each have a different rate of hydrolysis, enabling pulsed delivery of drug.

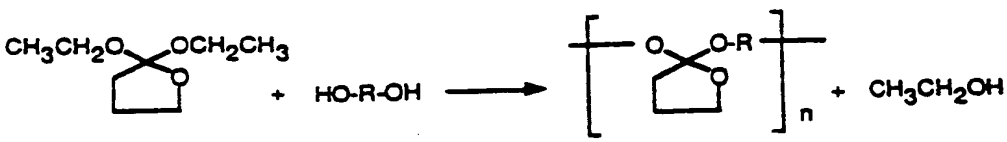
The paste-like bioerodible materials useful in conjunction with the present invention can be prepared by constructing polymer chains that have a great deal of flexibility in their backbones. A preferred embodiment of the present invention involves the use of bioerodible polymers that have highly flexible chains because such materials retain their paste-like consistency even though their molecular weight can be in excess of 50,000 Daltons.

Of particular interest are poly (ortho esters) because these materials contain the ortho ester linkage which is a highly flexible, hydrolytically labile, acid-sensitive linkage which allows, if deemed advantageous, adjustment in erosion rate by using either acidic or basic excipients.

A number of poly (ortho esters) have been described in the open and patent literature. However, their use in the pulsed delivery of high molecular weight

therapeutic agents, the subject of this invention, has not been described.

One means of preparing poly (ortho esters) has been described in U.S. Patent Nos. 4,093,709 and 4,131,648 to Choi and Heller, assigned to ALZA Corporation, Palo Alto, California. The polymers described in these patents are prepared by reaction of an ortho ester (or ortho carbonate) with a diol, as shown in Scheme 1.



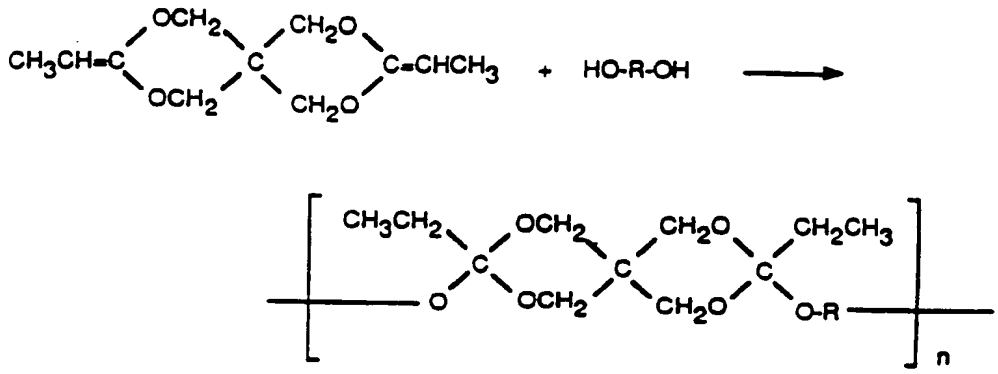
(I)

Scheme 1

The substituent "R" in compound (I), as set forth in the aforementioned patents, is preferably selected from the group consisting of alkylene of 1 to 10 carbon atoms, alkenylene of 2 to 10 carbon atoms, oxyalkylene of 2 to 6 carbon atoms, and cycloalkylene of 3 to 7 carbon atoms, wherein any of the aforementioned "R" groups may be either unsubstituted or substituted with a lower alkyl, lower alkoxy, lower alkylene or lower alkenyl group. The number "n" in compound (I) indicates the number of mer units in the polymer. When the substituent "R" contains six or more carbon atoms, soft, paste-like materials are obtained.

U.S. Patent No. 4,304,767 to Heller et al., assigned to SRI International, describes another method of preparing poly (ortho esters) which involves the

addition of polyols to diketene acetals, as exemplified in Scheme 2.

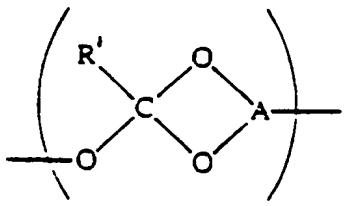


(II)

Scheme 2

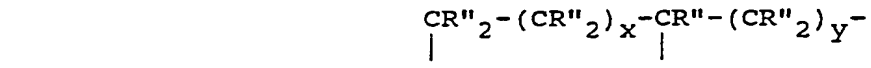
In compound (II), the substituent "R" is selected from the same group of moieties as set forth for "R" in compound (I), and "n" again indicates the number of mer units in the polymer. When the substituent "R" in these polymers contains about eight or more carbon atoms, soft, paste-like materials are obtained.

Still another poly (ortho ester) has been described in PCT Publication No. WO91/03510, inventors Heller et al. Those poly (ortho esters) contain mer units of the structure

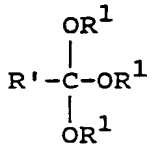


(III)

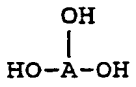
wherein R' is hydrogen or alkyl of 1 to 10 carbon atoms and A is selected from the group consisting of alkylenes and cycloalkylenes of at least 5 carbon atoms, oxyalkylenes and cyclooxyalkylenes of at least 5 carbon atoms, and alkylenes having the structure



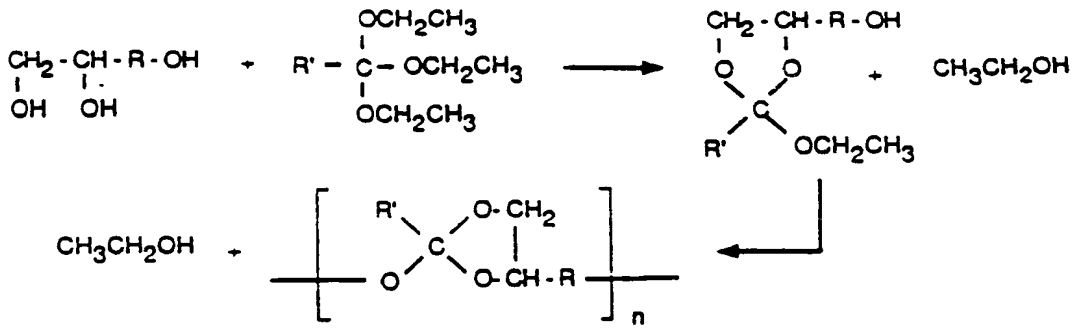
wherein x is 0 or 1, y is greater than or equal to 3, and the R"s are independently selected from the group consisting of hydrogen and lower alkyl. The number "n," as before, indicates the number of mer units in the polymer. As explained in the aforementioned PCT publication, these polymers may be synthesized by reacting a monomeric ortho ester having the general formula



wherein R is as defined above and the R' (which may be the same or different) is lower alkyl, with a triol having the general formula



wherein A is as defined previously. Scheme 3 exemplifies preparation of one subset of such polymers ("R" in Scheme 3 may be defined identically as in Schemes 1 and 2).



(IV)

Scheme 3

When the substituent "R" in these polymers contains on the order of three or more carbon atoms, soft, paste-like materials are obtained.

The disclosures of all of the aforementioned patents are incorporated by reference herein in their entireties, insofar as the polymers described in the various patents can be used to prepare the pharmaceutical compositions of the present invention.

Accordingly, the present invention addresses the need in the art for a pharmaceutical composition that is useful for administering high molecular weight therapeutic agents, e.g., polypeptide drugs. The invention provides such a composition which is a soft, paste-like material at room temperature or which has a low softening point, such that high molecular weight, sensitive therapeutic agents such as peptides can be incorporated into the composition under mild conditions. The composition contains at least one and preferably two or more such bioerodible polymers which hydrolyze at different rates. Two primary advantages are achieved in this way. First, there is little or no loss of

therapeutic effectiveness during incorporation of the drug, and second, pulsed delivery of drug is made possible.

Summary of the Invention

It is accordingly a primary object of the present invention to address the aforementioned need in the art, and to provide a bioerodible composition useful for the delivery of high molecular weight therapeutic agents, particularly peptide drugs.

It is another object of the invention to provide such pharmaceutical compositions as soft dosage forms, i.e., bioerodible ointments, gels, creams, and the like.

It is still another object of the invention to provide such pharmaceutical compositions which enable pulsatile drug delivery.

These objects are achieved by the present invention. In accordance with this invention, a pharmaceutical composition is provided for administering a therapeutic agent to a patient, the composition containing a therapeutic agent having a molecular weight greater than 1000 Daltons dispersed in and enclosed by a body of a hydrophobic, bioerodible polymer composition that is malleable at ambient temperatures and which undergoes bulk hydrolytic degradation at the conditions of use in the patient, and which restricts diffusion of the therapeutic agent from the polymer body prior to degradation and releases the active agent after the bulk degradation has occurred. In a preferred embodiment, the therapeutic agent is a peptide drug and the hydrophobic, bioerodible polymer composition comprises a plurality of poly (ortho ester) polymers.

In another aspect of the invention, a pharmaceutical composition is provided for pulsatile drug

delivery, the composition formulated so as to deliver an initial dose of a first therapeutic agent to be administered and a subsequent dose of a second therapeutic agent at a time spaced from the initial dose, wherein the composition comprises a first pharmaceutical carrier carrying the initial dose of the first therapeutic agent and a second pharmaceutical carrier carrying the subsequent dose of the second therapeutic agent. The first and second pharmaceutical carriers may be the same or different, and each comprise a hydrophobic, bioerodible polymer as defined above. The first and second therapeutic agents may be the same or different and each have a molecular weight greater than about 1000 Daltons. Again, the therapeutic agents are preferably peptide drugs and the bioerodible polymers are preferably poly (ortho esters).

In still another aspect of the invention, a pulsatile release pharmaceutical composition is provided which is capable of releasing a plurality "n" time-separated pulses of therapeutic agent to a patient, wherein the composition comprises an admixture of n delayed release pharmaceutical forms, each comprising therapeutic agent dispersed in and enclosed by a body of a hydrophobic, bioerodible polymer composition of the invention. Each of the n pharmaceutical forms is characterized as providing a different length of time, as compared with the other pharmaceutical forms in the composition, between administration to the patient and the time of release of its active agent.

Detailed Description of the Invention

Before describing the present invention in detail, it is to be understood that this invention is not limited to the particular drugs or polymers described herein as such may, of course, vary. It is also to be

understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting.

It must be noted that, as used in this specification and the appended claims, the singular forms "a," "an" and "the" include plural referents unless the content clearly dictates otherwise. Thus, for example, reference to "a drug" includes a mixture of two or more drugs, reference to "a carrier" includes reference to one or more carriers, and the like.

In describing and claiming the present invention, the following terminology will be used in accordance with the definitions set out below.

The term "bioerodible" as used herein to describe the polymers of the present invention is synonymous with the term of art "biodegradable." These terms denote the property of a body of solid gel polymer to undergo degradation, erosion and solubilization as a result of hydrolysis of labile linkages at the physiologic conditions of use.

The term "hydrophobic" as used herein to describe the bioerodible polymers in the compositions of the invention is intended to mean that the polymers have a lipophilic/hydrophilic balance as determined by an n-octane/water partition coefficient of at least about 1.0 and preferably at least about 2.0.

The term "drug" or "therapeutic agent" as used herein is intended to mean a compound or composition of matter which, when administered to an organism (human or animal) induces a desired pharmacologic and/or physiologic effect by local and/or systemic action. In general, the terms include the therapeutic or prophylactic agents in all major therapeutic/prophylactic areas of medicine. Examples of drugs useful in conjunction with the present invention include: anti-

infectives such as antibiotics and antiviral agents; analgesics and analgesic combinations; anorexics; antihelminthics; antiarthritics; antiasthmatic agents; anticholinergic agents; anticonvulsants; antidepressants; antidiabetic agents; antidiarrheals; antihistamines; anti-inflammatory agents, antimigraine preparations; anti-motion sickness drugs; antinauseants; antineoplastics; antiparkinsonism drugs; antipruritics; antipsychotics; antipyretics; antispasmodics; anticholinergics; sympathomimetics; xanthine derivatives; cardiovascular preparations including calcium channel blockers and beta-blockers such as pindolol and antiarrhythmics; antihypertensives; diuretics; vasodilators including general coronary, peripheral and cerebral; central nervous system stimulants; cough and cold preparations, including decongestants; steroids; hypnotics; immunosuppressives; muscle relaxants; parasympatholytics; psychostimulants; sedatives; and tranquilizers. The present invention, however, is primarily useful with high molecular weight, proteinaceous drugs or with drugs having relatively low solubility in water, e.g., buprenorphine, steroids such as hydrocortisone or levonorgestrel, or the like.

Preferred peptide drugs which may be administered using the present compositions include adrenocorticotropic hormone, angiotensin I-III, bovine serum albumin (BSA), bradykinins, dynorphins, endorphins, enkephalins, gastrin and gastrin-related peptides, bombesins, cholecystokinins, galanin, gastric inhibitory peptides, gastrin-releasing peptide, motilin, neuropeptide Y, pancreastatin, secretin, vasoactive intestinal peptide, growth hormone, growth hormone releasing factor (GRF), luteinizing hormone releasing hormone (LHRH), melanocyte stimulating hormones (MSH), neurotensins, nerve growth factor (NGF), oxytocin, vasopressin,

somatostatin, substance P, atrial natriuretic peptide (ANP), corticotropin releasing factors, epidermal growth factor, insulin, thymosin, calcitonin, urotensin, and the like. Other suitable peptides include animal growth factors and fragments of larger proteins, such as tissue plasminogen activator (tPA) and erythropoietin (EPO), and antigenic epitopes derived from infectious organisms, for example, peptides derived from malarial circumsporozoite antigens or chlamydia major outer membrane protein antigens.

By "high molecular weight" to describe the drugs with which the present compositions are most useful is meant a molecular weight of at least about 1,000 Daltons.

By "pulsed" or "pulsatile" drug delivery as used herein is meant intermittent drug delivery, i.e., the rate of drug release will peak at least once and preferably at least twice during an administration period. Typically, although not necessarily, the amount of drug released during an individual "pulse" is substantially similar to that released during other "pulses." In one embodiment of the invention, an initial dose of therapeutic agent is administered, i.e., a dose is delivered which does not involve a delay in drug release, followed by one or more subsequent "pulses" of drug release. The first of these pulses may be delayed on the order of hours, weeks or even months relative to the initial dose.

"Carriers" or "vehicles" as used herein refer to carrier materials without pharmacological activity which are suitable for administration in conjunction with the presently disclosed and claimed compositions, and include any such carrier or vehicle materials known in the art, e.g., any liquid, gel, solvent, liquid diluent, solubilizer, or the like. The carriers and vehicles

suitable herein are "pharmaceutically acceptable" in that they are nontoxic, do not interfere with drug delivery, and are not for any other reasons biologically or otherwise undesirable. Examples of specific suitable carriers and vehicles for use herein include water, mineral oil, silicone, inorganic gels, aqueous emulsions, liquid sugars, waxes, petroleum jelly, and a variety of other oils and polymeric materials.

The term "effective amount" as used herein intends that quantity of drug or therapeutic agent that, when administered to a patient, is required to provide the desired or intended beneficial effect without intolerable side effects, such as toxicity. When used in the context of controlled, prolonged or pulsed delivery of drug, the term can include a temporal aspect--noting that the rate of administration gives the desired effect without intolerable side effects.

The term "soft dosage form" as used herein is intended to mean a bioerodible ointment, gel, cream or the like, typically intended for topical administration of a drug. Dosage forms may be "soft" because of the nature of the polymer itself, i.e., the polymer selected for the dosage form may be ointment-like itself, or the dosage forms may be "soft" because of the incorporation of an ointment-like, gel-like or cream-like pharmaceutical carrier or vehicle.

The phrase "malleable at ambient temperatures" as used herein to describe the hydrophobic, bioerodible polymers of the invention is intended to mean that the polymers are soft or paste-like at room temperature or have a softening temperature of less than about 50°C.

The term "implantable" drug dosage form as used herein is intended to mean a drug-bearing polymeric body designed to be implanted subcutaneously or in a body

cavity so as to give rise to sustained release of the contained drug.

The term "lower alkyl" is intended to mean linear, branched or cyclic alkyl moieties having 1 to 6, and more typically 1 to 5, carbon atoms, inclusive.

The terms "alkylene," "alkenylene" and "cycloalkylene" have their usual meaning defining hydrocarbyl linking groups which serve as a bridge between two or more other groups.

The term "oxyalkylene" defines an aliphatic linking group containing one or more ether oxygens and providing two or more carbons as bridge points to other groups. Oxyalkylene groups can be linear, branched or cyclic.

Preferred polymers for use in conjunction with the present invention are those having the structures (I), (II), (III) or (IV) above. Particularly preferred polymers are those identified in PCT Publication No. WO91/03510, inventors Ng et al., cited and incorporated by reference above.

Typically, although not necessarily, the polymers of the invention have molecular weights of at least 1000 Daltons, typically ranging from several (2-3) thousand to 5,000-25,000 Daltons, but can have molecular weights as high as 50,000 Daltons or more. The polymers are hydrophobic in nature, malleable at ambient temperatures, and act to restrict diffusion of the therapeutic agent from the dosage form until hydrolyzed.

These polymers have the desirable properties of being able to undergo bioerosion, and of being generally paste-like at room temperature or having a softening point at temperatures less than about 50°C. Thus, the therapeutic agent to be administered can be simply admixed into the polymeric material at room temperature,

or at slightly elevated temperatures, to provide the desired dosage form.

Preferably, a plurality of polymers are selected for preparation of the pharmaceutical compositions of the invention such that they hydrolyze at different rates. Generally, higher molecular weight polymers hydrolyze more slowly, giving rise to a greater delay in release than lower molecular weight polymers. Also, poly (ortho esters) given by Formula (I) will be more readily hydrolyzed when the substituent "R" is smaller and less readily hydrolyzed when "R" is larger. Thus, typically, the compositions of the invention will involve polymers of differing molecular weight and/or poly (ortho esters) as defined in Formula (I) having differently sized "R" substituents.

Suitable therapeutic agents which may be administered using the present compositions and methods are as outlined above. Preferred therapeutic agents are, however, high molecular weight proteinaceous drugs, including, but not limited to, those identified above. The present compositions may be formulated so that there is a one-to-one correlation between each individual polymer and each drug selected for administration, e.g., individual polymer/drug combinations are admixed with other such combinations to provide the complete composition. Each such pharmaceutical "form"--i.e., each polymer/drug combination which exists as an individual entity--is delayed release in nature, with each individual form providing a different length of time between administration to the patient and the time of release of its active agent. Alternatively, one of the forms may be non-delayed release in nature, such that an initial dose of therapeutic agent is delivered, followed by one or more subsequent, "pulsed" doses.

These formulations are prepared by admixing each selected therapeutic agent with a corresponding hydrophobic, bioerodible polymer as described above, with the polymer selected so as to provide the desired time delay for drug release. Generally, each such form will be paste- or ointment-like, resulting in a soft composition containing the plurality of dosage forms. The composition may be administered as is, or it be formulated with suitable carriers as a gel, cream, or the like, or it may be prepared as a solid implant, or as microcapsules.

Preparation of solid implants or microcapsules may be effected using conventional techniques, as will be appreciated by those skilled in the art. Preferred solid implants comprise a macroporous shell which serves to confine the polymer/drug composition, and, when more than one such composition or form is present, the shell confines the individual forms as discrete domains. The macroporous shell is such that aqueous contact is maintained between the contained polymer/drug formulations and the surrounding environment, enabling unimpeded diffusion. Such a solid implant is prepared by admixing the individual polymer/drug forms and filling the shell with each form, sequentially. Microcapsules are prepared, typically, either by a coacervation technique (in which drug/polymer forms are admixed, introduced into alginate, emulsified with an organic solvent, and then precipitated) or via a crosslinking step (involving formation of a first emulsion with chitosan, a second emulsion with, e.g., cold hexane, followed by treatment with a suitable crosslinking agent). Such techniques are described, for example, in Lim et al., J. Pharm. Sci. 70(4):351-353 (1981) and in Wisseman et al., In Vitro Cellular & Developmental

Biology 21(7):391-401 (1985), the disclosures of which are incorporated by reference herein.

The compositions of the invention may also include one or more other components, e.g., nontoxic auxiliary substances such as colorants, diluents, odorants, carriers, excipients, stabilizers or the like. Conventional nontoxic carriers include, for example, pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharin, talcum, cellulose, glucose, sucrose, magnesium carbonate, and the like.

The amount of active agent will be dependent upon the particular drug employed and the condition being treated. Typically the amount of drug in every pharmaceutical form, i.e., in each individual polymer/drug admixture within the present compositions, is about 0.001% to about 70%, more typically about 0.001% to about 50%, most typically about 0.001% to about 20% by weight of the total, individual drug/polymer form.

While not essential for topical or transdermal administration of many drugs, it may in some cases, with some drugs, be preferred that a skin permeation enhancer be coadministered therewith. Any number of the many skin permeation enhancers known in the art may be used. Examples of suitable enhancers include dimethylsulfoxide (DMSO), dimethylformamide (DMF), N, N-dimethylacetemide (DMA), desylmethylsulfoxide (C_{10}MSO), ethanol, eucalyptol, lecithin, and the 1-N-dodecylcyclazacyclo-heptan-2-ones (available under the trademark Azone® from the Nelson Research and Development Company, Irvine, California).

It is additionally preferred to incorporate either an acidic or basic excipient, typically an acidic excipient, into the present compositions in order to control the rate of polymer bioerosion. The ortho ester linkages of the bioerodible polymers are typically

relatively stable at basic or neutral pH and are hydrolyzed at progressively increasing rates as the pH of the medium surrounding the polymer decreases. Thus, hydrolytic lability and the rate of erosion and drug release can be increased by incorporation of one or more acidic components. Preferred acidic excipients are aliphatic acids, typically present at 0-10 wt%, more preferably 1-5 wt%, of the bioerodible composition. Solid but water soluble aliphatic acids are generally favored. Examples of acidic excipients useful in conjunction with the present invention include adipic, citric, suberic, maleic and itaconic acids. Basic excipients, e.g., sodium carbonate, potassium carbonate, potassium bicarbonate, magnesium hydroxide, calcium lactate, or the like, may also be used to slow the rate of release.

Administration of therapeutic agents using the present compositions will result in pulsatile drug delivery over a prolonged delivery period (over, typically, 1 to 10,000 hours, preferably 2 to 1000 hours) of effective amounts (normally 0.0001 mg/kg/hour to 10 mg/kg/hour) of drug. Application can be repeated as necessary depending on the subject being treated, the therapeutic agents being administered, the severity of the affliction, the judgment of the prescribing physician, and the like.

The examples presented below are provided as a further guide to the practitioner of ordinary skill in the art, and are not to be construed as limiting the invention in any way.

Example 1

The effect of molecular weight of the bioerodible polymer on the drug release profile was evaluated as follows. Lysozyme was incorporated via

simple admixture at room temperature into propionate poly (ortho esters) as shown in Scheme 3, where the substituent R' was $CH_3CH_2CH_2$-. To evaluate drug release, phosphate buffer, pH 7.4, thermostated at 37°C, was pumped across the drug-containing ointment compositions at 9.55 cc/hr and collected in tubes for subsequent analysis. Polymers of three different molecular weights were tested: 3200 Daltons, 4,600 Daltons and 6,600 Daltons.

Results are summarized graphically in Figure 1. As may be deduced therefrom, the polymer having a molecular weight of 3,200 released the protein in an essentially linear fashion, the polymer having a molecular weight of 4,600 released the protein after a two-day induction period and the polymer having a molecular weight of 6,600 released the protein after a four-day induction period. Those skilled in the art will appreciate that the induction period can be significantly increased by further increases in the molecular weight of the polymer.

The pulsatile delivery profile obtained by admixture of the individual polymer/drug formulations is plotted in Figure 2.

Example 2

In this example, the effect of the size of the substituent R' on delay time was evaluated using the technique set forth in the preceding example. Lysozyme was incorporated into valerate polymers of molecular weight 5500 Daltons and 9300 Daltons. The polymers were the poly (ortho esters) of Scheme 3 wherein R' is $CH_3CH_2CH_2CH_2CH_2$-. Results are set forth in Figure 3.

As may be seen in the figure, there is again the effect of molecular weight. However, there is also a very significant effect of the size of the R' group on

delay time, and a polymer that has a molecular weight of 9,300 has a delay time of over one month.

Example 3

The procedure of Example 1 may be repeated using bovine serum albumin (BSA). Substantially the same pulsatile release profile as obtained in Example 1 will result.

Example 4

The procedure of Example 1 may be repeated using amylase. Substantially the same pulsatile release profile as obtained in Example 1 will result.

Example 5

The procedure of Example 1 may be repeated using human fibroblast growth factor. Substantially the same pulsatile release profile as obtained in Example 1 will result.

Example 6

The procedure of Example 2 may be repeated using a valerate polymer as prepared in Scheme 3, wherein R' is ethyl. The drug/polymer composition prepared using this polymer will result in a much shorter delay time than when R' is n-pentyl.

Example 7

The procedure of Example 2 may be repeated using a valerate polymer as prepared in Scheme 3, wherein R' is n-hexyl. The drug/polymer composition prepared using this polymer will result in a much longer delay time than when R' is n-pentyl.

Example 8

The polymer/drug compositions of Example 1 may be used to fill a 2x10 mm rod-type solid implant having a shell of lactic/glycolic acids (50/50). Substantially the same pulsatile release profile of Figure 2 is obtained.

Example 9

The polymer/drug compositions of Example 1 may be used to prepare microcapsules, as follows. The polymer/drug formulations are uniformly suspended in a 0.6% sodium alginate solution prepared in saline. Droplets containing the compositions may then be produced by extrusion through a capillary tip and dropped into a beaker containing 1.5% calcium chloride solution. The calcium ions will cause immediate gelling of each droplet. The microcapsules thus formed may be harvested by decantation and processed further to impart a permanent semi-permeable membrane by suspension in a 0.02% polylysine solution for 3-5 minutes.

Alternatively, microcapsules may be prepared by emulsifying the polymer/drug compositions of Example 1 into chitosan, then emulsifying the chitosan with cold hexane, followed by crosslinking with glutaraldehyde.

CLAIMS

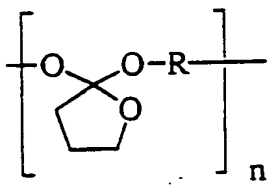
1. A pharmaceutical composition for administration to a patient, comprising a therapeutic agent having a molecular weight greater than approximately 1000 Daltons dispersed in and enclosed by a body of a hydrophobic, bioerodible polymer composition that is malleable at ambient temperatures and which undergoes bulk hydrolytic degradation at the conditions of use in the patient, and which restricts diffusion of the therapeutic agent from the polymer body prior to degradation and which releases the active agent after the bulk degradation has occurred.

2. The composition of claim 2 wherein the therapeutic agent is a peptide.

3. The composition of claim 1 wherein the hydrophobic polymer composition comprises a plurality of poly (ortho ester) polymers.

4. The composition of claim 2 wherein the bioerodible hydrophobic polymer composition comprises a plurality of poly (ortho ester) polymers.

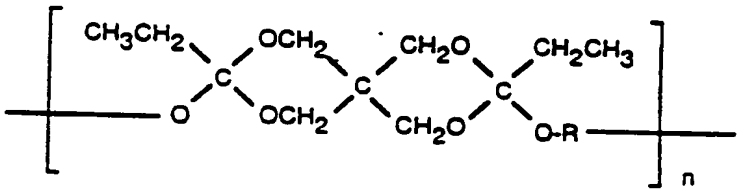
5. The composition of claim 3 wherein at least one of said poly (ortho ester) polymers contains repeating mer units having the structure



wherein R is selected from the group consisting of alkylene of 1 to 10 carbon atoms, alkenylene of 2 to 10 carbon atoms, oxyalkylene of 2 to 6 carbon atoms, and cycloalkylene of 3 to 7 carbon atoms, and may be either unsubstituted or substituted with a lower alkyl, lower alkoxy, lower alkylene or lower alkenyl group, and "n" indicates the number of mer units in the polymer.

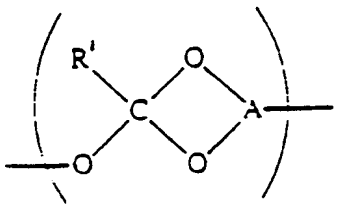
6. The composition of claim 3 wherein at least one of said poly (ortho ester) polymers is of a polyol and a diketene acetal and has a functionality of two or more.

7. The composition of claim 6 wherein said at least one polymer contains repeating mer units having the structure

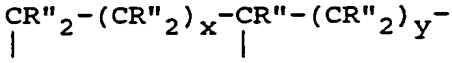


wherein R is selected from the group consisting of alkylene of 1 to 10 carbon atoms, alkenylene of 2 to 10 carbon atoms, oxyalkylene of 2 to 6 carbon atoms, and cycloalkylene of 3 to 7 carbon atoms, and may be either unsubstituted or substituted with a lower alkyl, lower alkoxy, lower alkylene or lower alkenyl group, and "n" indicates the number of mer units in the polymer.

8. The composition of claim 3 wherein at least one of said poly (ortho ester) polymers contains repeating mer units having the structure

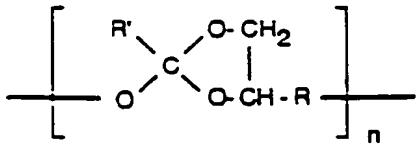


wherein R' is hydrogen or alkyl of 1 to 10 carbon atoms, A is selected from the group consisting of alkylenes and cycloalkylenes of at least 5 carbon atoms, oxyalkylenes and cyclooxyalkylenes of at least 5 carbon atoms, and alkylenes having the structure



wherein x is 0 or 1, y is greater than or equal to 3, and the R"s are independently selected from the group consisting of hydrogen and lower alkyl, and "n" represents the number of mer units in the polymer.

9. The composition of claim 3 wherein at least one of said poly (ortho ester) polymers contains repeating mer units having the structure



wherein R' is hydrogen or alkyl of 1 to 10 carbon atoms, R is selected from the group consisting of alkylene of 1 to 10 carbon atoms, alkenylene of 2 to 10 carbon atoms, oxyalkylene of 2 to 6 carbon atoms, and cycloalkylene of 3 to 7 carbon atoms, and may be either unsubstituted or

substituted with a lower alkyl, lower alkoxy, lower alkylene or lower alkenyl group, and "n" indicates the number of mer units in the polymer.

10. The composition of claim 3 in the form of an ointment.

11. The composition of claim 3 in the form of a gel.

12. The composition of claim 3 in the form of a cream.

13. The composition of claim 3 in the form of a solid implant.

14. The composition of claim 3 in the form of microspheres.

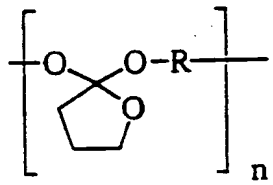
15. A pharmaceutical composition for delivering an initial dose of a first therapeutic agent to a patient and a subsequent dose of a second therapeutic agent at a time spaced from the initial dose, wherein the composition comprises a first pharmaceutical carrier carrying the initial dose of the first therapeutic agent and a second pharmaceutical carrier carrying the subsequent dose of the second therapeutic agent, wherein the first and second pharmaceutical carriers may be the same or different and comprise a hydrophobic, bioerodible polymer composition that is malleable at ambient temperatures and which undergoes bulk hydrolytic degradation at the conditions of use in the patient, and wherein the first and second therapeutic agents may be the same or different and each have a molecular weight greater than approximately 1000 Daltons.

16. The composition of claim 15 wherein the initial dose is in non-time-delayed form and the subsequent dose is in delayed release form.

17. The composition of claim 15 wherein the first and second therapeutic agents are peptides.

18. The composition of claim 15 wherein the hydrophobic, bioerodible polymer composition comprises a plurality of poly (ortho ester) polymers.

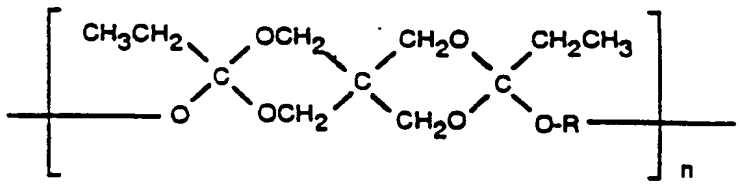
19. The composition of claim 15 wherein at least one of said poly (ortho ester) polymers contains repeating mer units having the structure



wherein R is selected from the group consisting of alkylene of 1 to 10 carbon atoms, alkenylene of 2 to 10 carbon atoms, oxyalkylene of 2 to 6 carbon atoms, and cycloalkylene of 3 to 7 carbon atoms, and may be either unsubstituted or substituted with a lower alkyl, lower alkoxy, lower alkylene or lower alkenyl group, and "n" indicates the number of mer units in the polymer.

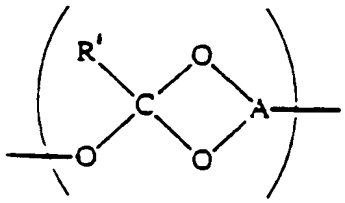
20. The composition of claim 15 wherein at least one of said poly (ortho ester) polymers is of a polyol and a diketene acetal and has a functionality of two or more.

21. The composition of claim 15 wherein said at least one polymer contains repeating mer units having the structure

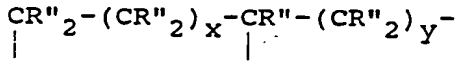


wherein R is selected from the group consisting of alkylene of 1 to 10 carbon atoms, alkenylene of 2 to 10 carbon atoms, oxyalkylene of 2 to 6 carbon atoms, and cycloalkylene of 3 to 7 carbon atoms, and may be either unsubstituted or substituted with a lower alkyl, lower alkoxy, lower alkylene or lower alkenyl group, and "n" indicates the number of mer units in the polymer.

22. The composition of claim 15 wherein at least one of said poly (ortho ester) polymers contains repeating mer units having the structure

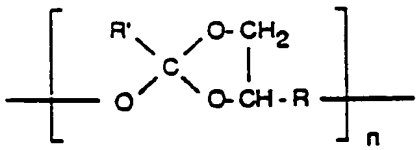


wherein R' is hydrogen or alkyl of 1 to 10 carbon atoms, A is selected from the group consisting of alkylenes and cycloalkylenes of at least 5 carbon atoms, oxyalkylenes and cyclooxyalkylenes of at least 5 carbon atoms, and alkylenes having the structure



wherein x is 0 or 1, y is greater than or equal to 3, and the R"s are independently selected from the group consisting of hydrogen and lower alkyl, and "n" represents the number of mer units in the polymer.

23. The composition of claim 15 wherein at least one of said poly (ortho ester) polymers contains repeating mer units having the structure



wherein R' is hydrogen or alkyl of 1 to 10 carbon atoms, R is selected from the group consisting of alkylene of 1 to 10 carbon atoms, alkenylene of 2 to 10 carbon atoms, oxyalkylene of 2 to 6 carbon atoms, and cycloalkylene of 3 to 7 carbon atoms, and may be either unsubstituted or substituted with a lower alkyl, lower alkoxy, lower alkylene or lower alkenyl group, and "n" indicates the number of mer units in the polymer.

24. The composition of claim 15 in the form of an ointment.

25. The composition of claim 15 in the form of a gel.

26. The composition of claim 15 in the form of a cream.

27. The composition of claim 15 in the form of a solid implant.

28. The composition of claim 15 in the form of microspheres.

29. A pharmaceutical composition capable of releasing a plurality n of time-separated pulses of therapeutic agent to a patient, said composition comprising an admixture of n delayed release pharmaceutical forms, each comprising therapeutic agent having a molecular weight greater than approximately 1000 Daltons dispersed in and enclosed by a body of a hydrophobic, bioerodible polymer composition that is malleable at ambient temperatures and which undergoes bulk degradation at the conditions of use in the patient, and which restricts diffusion of therapeutic agent from the polymer body prior to degradation and which releases the therapeutic agent after the bulk degradation has occurred, with each of the n pharmaceutical forms being characterized as providing a different length of time, as compared to the other forms, between administration to the patient and the time of release of its active agent.

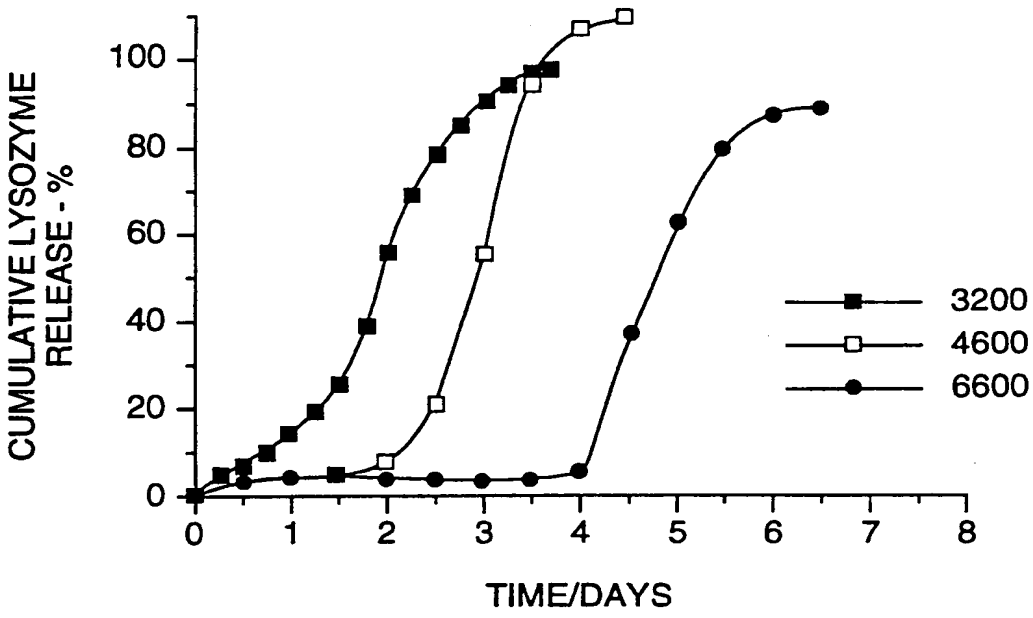

CUMULATIVE LYSOZYME RELEASE - %
100
80
60
40
20
0
0
1
2
3
4
5
6
7
8
TIME/DAYS
3200
4600
6600

FIG. 1

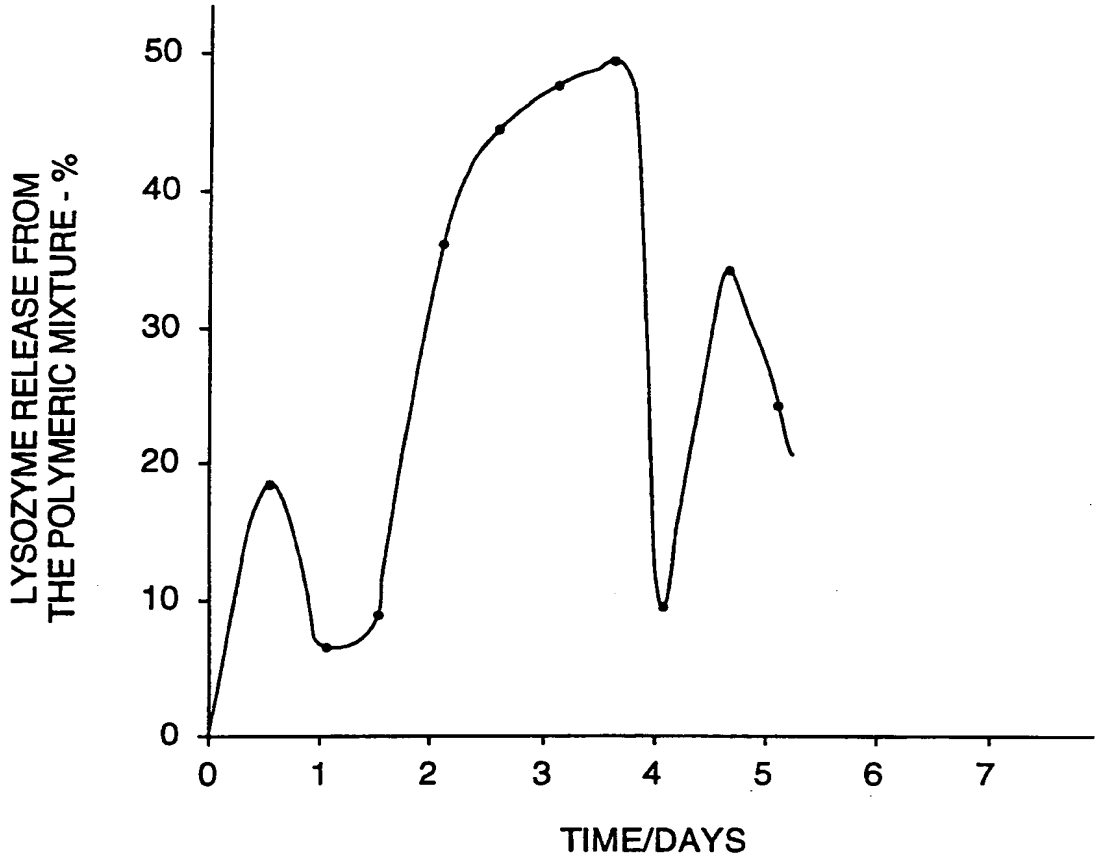

LYSOZYME RELEASE FROM THE POLYMERIC MIXTURE - %
50
40
30
20
10
0
0
1
2
3
4
5
6
7
TIME/DAYS

FIG. 2

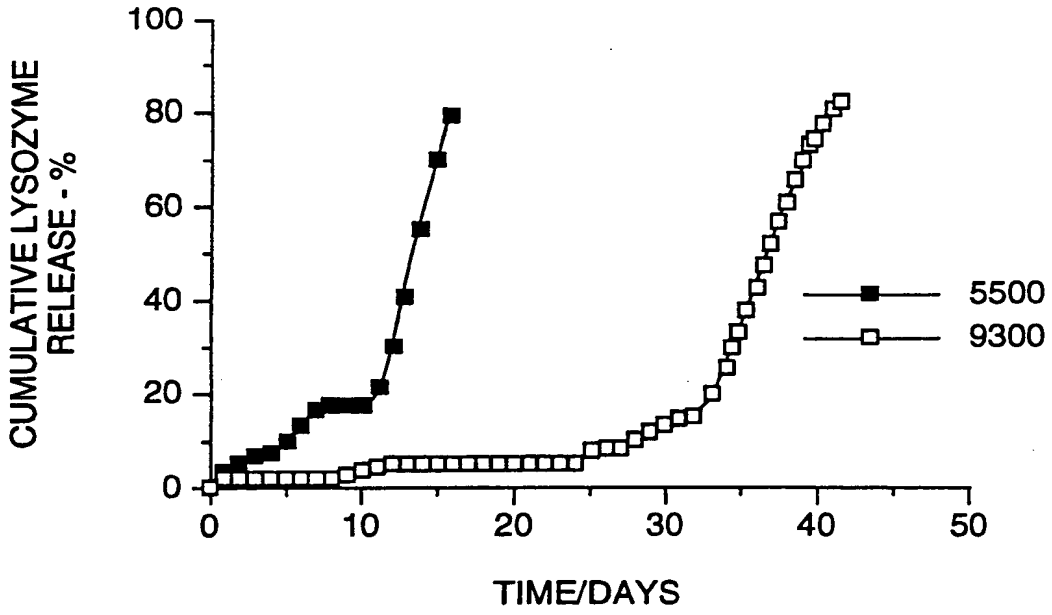

CUMULATIVE LYSOZYME RELEASE - %
100
80
60
40
20
0
0
10
20
30
40
50
TIME/DAYS
5500
9300

FIG. 3

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US92/05195

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :C08G 65/34; A61K 9/06, 9/107
US CL :424/426
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/486

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

NONE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US, A, 5,030,457 (NG ET AL.) 09 JULY 1991, entire document	1-29
A	US, A, 4,093,709 (CHOI ET AL.) 06 JUNE 1978, entire document	1-29

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be part of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 06 AUGUST 1992	Date of mailing of the international search report 27 OCT 1992
Name and mailing address of the ISA/ Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. NOT APPLICABLE	Authorized officer RAJ BAWA Telephone No. (703) 308-2351

Form PCT/ISA/210 (second sheet)(July 1992)★